ASSOCIATION BETWEEN WOMAC SCORE AND 2D:4D RATIO IN WOMEN WITH KNEE OSTEOARTHRITIS

BY

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LIST OF ABBREVIATIONS

OA	**osteoarthritis**
WOMAC	**Western Ontario and McMaster Osteoarthritis Index**
WOMAC-LK	**Western Ontario and McMaster Osteoarthritis Index likert**
WOMAC-VA	**Western Ontario and McMaster Osteoarthritis Index visual analogue**
COPCORD	**Community Orientated Program for the control of Rheumatic Disease**
ACR	**American Collage of Rheumatology**
ESR	**Erythrocyte sedimentation rate**
SF –OA	**synovial fluid osteoarthritis**
CPG	**clinical practice guidelines**
2D:4D	**second digit: forth digit**
WHO	**World Health Organization**
BMI	**Body Mass Index**
NHANES	**National Health and Nutrition Examination Survey**
JSN	**Joint space narrowing**

ABSTRAK

Pendahuluan: Isu utama pada osteoartritis adalah risiko untuk mengalami simptom sakit berterusan dan kelemahan aktiviti fizikal. Osteoartritis sendi lutut merupakan salah satu masalah sendi utama yang menyebabkan kelemahan aktiviti fizikal. Wanita lanjut umur lebih mengalami pengurangan kadar kualiti kehidupan disebabkan oleh masalah tersebut. Faktor utama yang menyebabkan kelemahan aktiviti fizikal adalah peningkatan umur, berat badan berlebihan dan obesiti, kurang bersenam, mempunyai sejarah kecederaan sendi dan masalah kesihatan yang lain.

Nisbah digit 2D:4D merupakan penanda dimorfik jantina. Secara umum, lelaki mempunyai nisbah 2D:4D yang rendah bermaksud jari telunjuk lebih panjang dari jari manis .Manakala wanita mempunyai nisbah 2D:4D yang tinggi atau sama, bermaksud jari telunjuk lebih rendah daripada jari manis atau sama kepanjangannya. Perbezaan nisdah digit ini berkaitan dengan keupayaan fizikal, sikap dan bentuk fizikal. Kajian sebelum ini menunjukkan perkaitan nisbah digit dengan osteoarthritis sendi lutut, di mana nisbah 2D:4D yang rendah menpunyai risiko yang tinggi untuk mengalaminya.

Objektif: Untuk menentukan perkaitan antara skor WOMAC, indek jisim tubuh (BMI) dengan nisbah 2D:4D pada wanita yang mengalami osteoarthritis sendi lutut gred 2 dan 3.

Kaedah kajian: Kami menjalankan kajian secara keratan rentas yang melibatkan 118 wanita yang mengalami osteoarthritis sendi lutut (Kellgren Lawrence 2 – 3). Peserta akan mengisi borang soal selidik WOMAC. Panjang jari telunjuk dan jari manis diukur dari X ray tangan kanan. Peserta diklasifikasikan kepada tiga kumpulan iaitu jenis I (jari telunjuk lebih panjang dari jari manis), jenis II (kedua duanya sama panjang) dan jenis

III (jari telunjuk lebih pendek dari jari manis). Indek jisim tubuh (BMI) diukur dan dicatatkan mengikut piawaian yang ditetapkan.

Keputusan: Kebanyakkan daripada peserta diklasifikasikan dalam jenis ketiga n=56 (47%). Walaubagaimanapun, kajian menunjukkan tiada perkaitan antara skor WOMAC dan setiap komponennya dengan nisbah 2D:4D. Terdapat kolerasi antara indek jisim tubuh (BMI) dengan gejala sendi lutut yang teruk berdasarkan skor WOMAC (p-value<0.001, r = 0.643). Terdapat perkaitan yang jelas antara nisbah 2D:4D dengan indek jisim tubuh (BMI) (F-stat (df) 4.38 (2), P-value 0.015) .Majoriti yang mempunyai indek jisim tubuh (BMI) yang lebih tinggi berada dalam kumpulan jenis II (mean (SD) 30.2 (4.31)).

Kesimpulan: Tiada perkaitan di antara skor WOMAC dengan nisbah 2D:4D pada wanita yang mengalami osteoarthritis sendi lutut gred 2 dan 3. Ini bermakna perbezaan jenis nisbah digit tidak menjejaskan tahap keterukan keupayayan fizikal. Walaubagaimanapun, kajian menunjukkan terdapat kolerasi positif antara skor WOMAC dengan indek jisim tubuh (BMI) dan juga perkaitan antara nisbah 2D:4D dan indek jisim tubuh (BMI) yang lebih tinggi. Majoriti peserta yang mempunyai indek jisim tubuh (BMI) yang tinggi berada dalam kumpulan jenis II.

ABSTRACT

Introduction: The main issue in osteoarthritis is the risk of pain and physical disability. Knee osteoarthritis is one of the commonest joint disorders that lead to physical disability. Elderly women experience lower quality of life due to functional limitation and physical disability than male. Main factor that cause physical disability are increasing age, obesity, lack of exercise, previous knee injury and medical comorbidity.

In human, finger length ratio (2D:4D) is a sexually dimorphic trait. Generally, males have low 2D:4D ratio; a ring finger that is longer than their index finger. While female typically have high or equal 2D: 4D ratio, index finger longer than ring fingers or the same length. Different digit ratio associated with human physical capability, attitude and characteristic. Previous study suggested that low 2D:4D ratio associated with higher risk to developed knee osteoarthritis in women.

Objectives: To determine association between WOMAC score, Body Mass Index (BMI) with 2D:4D ratio in women with grade 2 and 3 of knee osteoarthritis.

Patients and Methods: We conducted cross sectional study in 118 women with knee osteoarthritis (Kellgren Lawrence grade 2 -3), who completed the Western Ontario and McMaster Osteoarthritis Index (WOMAC) questionnaire. Length of index finger and ring finger were measured from right hand radiographs. Subjects were classified into three groups: type I (index finger longer than ring finger), type II (equal length) and type III (index finger shorter than ring finger). Body Mass Index (BMI) was measured and recorded by standard procedure.

Result: The majority of the participants were classified under type III finger pattern n=56 (47%). However, this study showed there was no significant mean difference between mean total WOMAC score and each component with 2D:4D ratio. BMI correlated significantly with worse knee OA symptoms for total WOMAC score (p-value<0.001, r = 0.643). There was a significant association between 2D:4D ratio and Body Mass Index (BMI) (F-stat (df) 4.38 (2), P-value 0.015) and higher BMI majority in type II (mean (SD) 30.2 (4.31)).

Conclusion: There is no association between WOMAC score and 2D:4D ratio in women with grade 2 and 3 of knee osteoarthritis. It means that different type of finger pattern does not affect the severity of physical disability. However, the study showed positive correlation between total WOMAC score and higher Body Mass Index (BMI) and significant association between 2D:4D ratio and higher Body Mass Index (BMI). Those with higher Body Mass Index (BMI) majority in type II

1.0 INTRODUCTION

Osteoarthritis (OA) is a progressive joint disease due to failure in repair of joint damage. It occurs mainly over the tibiofemoral joint (knee joint). Elderly age and female gender contribute to main risk factor of knee osteoarthritis. BMI and previous knee trauma are also known risk factor for OA knee (Lawrence et al 1998, Hick et al 2001).

The prevalence among women with radiology evidence of OA are higher compared to male. Studies had been done to find the cause of this fact and showed various result.

The main issue with osteoarthritis of the lower limb is physical disability (Toresss et al 2006). It is one of the commonest joint disorders that lead to physical disability in the elderly. Although elderly women experience lower rate of chronic disease and longer life span, it has been reported that they have lower quality of life due to functional limitation and physical disability than male (McAlion 1993).

Disability among gender differences remained unexplained although some study tried to associate it with demographic factors, chronic disease, osteoarthritis and joint disease. (Kristen et al, 2011).

On the other hand, previous studies showed that there is no relationship between radiological evidence with symptom of knee osteoarthritis (Creamer et al 2000). Study by Larson et al 1998, reported radiographic evidence of knee was not related to functional capacity and disability among patient with knee OA. It was supported by Gucceion, whereby a patient can be presented with radiographic evidence of knee OA with absence of poor ability to perform activities (Gucceion et al 1990).

In general, there is limited association between the disease process of osteoarthritis of knee and the syndrome of musculoskeletal pain and disability (Salaffi et al 1991,Fries et al 1997, Vita et al 1998).

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is widely used in the evaluation of Hip and Knee osteoarthritis. It was developed in 1982 at Western Ontario and McMaster Universities. The WOMAC has been extensively used in both observational and epidemiological studies and to assess improvement in patient with post treatment intervention.

The use of the WOMAC has also been validated in many medium, including through questionnaire and via phone or computer. It is proven to be valid, reliable, efficient and responsive (Mc Connell et al 2001). It is a self-administered questionnaire consisting of 24 items divided into 3 subscales. Pain (5 subset), stiffness (2 subset) and disability (17 subset). On the Likert Scale version, the scores are summed for items in each subscale: pain (0-20), stiffness (0-8) and disability (0-68). The higher the score indicates worsening in pain, stiffness and limited functional ability.

Anthropological studies had suggested that there are consistency between sex differences with the ratio of the lengths of the index finger (2D) and the ring (4D) finger (Manning et al 1998, Honekoop et al 2010).

Generally, males have a ring finger that longer than their index finger while female typically have index finger longer than ring finger or same. The discrepancy between length of index and ring finger reflecting exposure of prenatal testosterone, whereby low 2D:4D ratio indicates higher of exposure in utero testosterone (Manning et al 1998, Mcintyre et al 2006, Lutchmaya et al 2004).

Visually, 2D: 4D finger length ratio can be classified into three types, 1) type I is when index finger longer than ring finger, 2) type II; index finger equal to ring finger and 3) type III ; index finger shorter than ring finger (Zhang et al 2008).

Previous studies of 2D:4D ratio and the risk of knee OA showed inconsistent result. Zhang and Ferraro concluded that type III associated with risk of knee OA in women (Zhang et al 2008, Ferraro et al 2010).

This study is done to look at the association between symptomatic of knee OA in difference perspective and components (pain, stiffness and disability) with 2D:4D finger length ratio specifically in women. In addition, we also look at any correlation between WOMAC score and BMI and any significant correlation between BMI and 2D:4D ratios.

Functional disability in knee OA has been shown to highly correlate with high BMI. Since finger pattern type III for 2D:4D ratio in female is known to have high risk of getting knee OA, we want to see if there any relation between 2D:4D ratio with BMI.

2.0 LITERATURE REVIEW

2.1 KNEE OSTEOARTHRITIS

2.1.1 OVERVIEW OF KNEE OSTEOARTHRITIS

Osteoarthritis is the most common form of arthritis and it is a major cause of disability in middle age and older people. The common joint affected is the knee joint (Peta G et al 2002).

In the Global Burden of Disease 2010 Study, it was estimated that 251 million people suffered from knee OA worldwide. Musculoskeletal diseases which included OA was the second greatest cause of disability as measured by years lived with disability.

Elderly patient come to the clinic with severe progressive knee pain and disability whether it is due to the knee pain or reduced quadriceps strength due to functional impairment with poor correlation with radiological finding (Sasse et al 1989, Mc Alindon et al 1993).

The COPCORD (Community Orientated Program for the control of Rheumatic Disease) 1997 study in Malaysia showed that 9.3% of adult Malaysians complained of knee pain with a sharp increase in pain rate to 23% in those over 55 years of age and 39% in those over 65 years.

2.1.2 DIAGNOSIS OF KNEE OSTEOARTHRITIS

Primary knee or idiopathic knee osteoarthritis can be diagnosed based on symptom and clinical assessment. In the past, diagnosis of osteoarthritis often based on radiographic knee rather to clinical assessment as the plain radiograph remains the most available indirect method to detect articular changes. However imaging technique does not define the clinical symptoms of osteoarthritis, since up to 40 % of patients with radiological changes of OA are not symptomatic. Furthermore, knee pain, stiffness and duration of illness have more effect to level of disability in patient which subsequently effects the management when compared to radiological finding (Duygu et al 2012).

The most common presenting complaint in middle age to elderly person is knee pain. It can occur insidiously with variable intensity throughout the day. It is aggravated by joint use and its impact and relieved by rest; moreover night pain can occur in severe osteoarthritis.

Stiffness (sensation of tightening of knee or other joint) can occur after inactivity or early morning once wake up from sleep and after prolong sitting. Joint swelling can occur due to effusion around the knee joint or bony swelling. Other symptoms are deformity of knee (genu varus or genu valgus) with loss of stability which subsequently cause patient use ambulatory assistant such as cane.

Effusion, deformity and crepitus can confirmed by clinical examination of the knee joint. Ligamentous laxity is varied depending on the severity. Limitation range of motion may also be affected which can cause disruption in daily activity other than pain. Generally, osteoarthritis of the knee does not manifest any of other cardinal sign of inflammation such as redness or raise of temperature (Altman et al 1986).

The development of criteria for the classification of OA present a particular problem because of the nonspecific nature of disease, high proportion of asymptomatic patients and the lack of a diagnostic test (Altman et al 1986).

The diagnostic criteria for classification of knee OA are based on the American College of Rheumatology (ACR) criteria. It is based on recognised subset of knee OA and subset of OA which are identified with combination of clinical and laboratory findings.

Table 2: Diagnostic criteria for classification of knee OA are based on the American College of Rheumatology (ACR) 1986 criteria.

Diagnosis / Criteria	Clinical and laboratory	Clinical and radiographic	Clinical only	
Must have	Knee pain + At least 5 of 9 of the following	Knee pain + Osteophytes on x-ray + At least 1 of 3 of the following	Knee pain + At least 3 of 6 of the following	
1	Age >50 years	Age >50 years	Age >50 years	
2	Stiffness <30 min	Stiffness <30 min	Stiffness <30 min	
3	Crepitus	Crepitus	Crepitus	
4	Bony tenderness		Bony tenderness	
5	Bony enlargement		Bony enlargement	
6	No palpable warmth		No palpable warmth	
7	ESR <40			
8	RF <1: 40			
9	SF OA			
Sensitivity **Specificity**	92% 75%	91% 86%	95% 69% (if 3/6)	84% 89% (if 4/6)

ESR=erythrocyte sedimentation rate RF=rheumatoid factor
SF OA=synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/mm³)

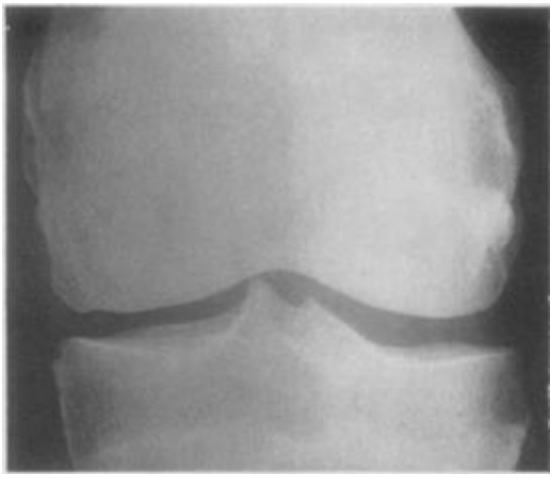
Knee osteoarthritis is also diagnosed using evidence base recommendation by The European League Against Anti Rheumatism (EULAR) in 2010. From their recommendation, in diagnostic knee osteoarthritis, three symptoms (persistent knee pain, limited morning stiffness and reduced function) and three signs (crepitus, restricted movement and bony enlargement) appeared to be the most useful. The sensitivity and specificity are up to 99% with positive background of risk factor and adult age same or more than 45 years old adjunct with radiological appearance (Zhang W et al 2010).

2.1.3 RADIOLOGICAL CLASSIFICATION OF KNEE OSTEOARTHRITIS

Plain radiograph are commonly used by orthopaedic surgeon when planning surgical treatment. The Kellgren Lawrence classification is the most widely used and practical classification in clinical setting. It is based on assessment of difference observer in reading x ray in osteoarthritis (finger, hip, wrist and knee). For knee, they use anteroposterior weight bearing knee. (J.H. Kellgren and J.S Lawrence et al 1957).This method of classified the severity of knee osteoarthritis (OA) into five grades.

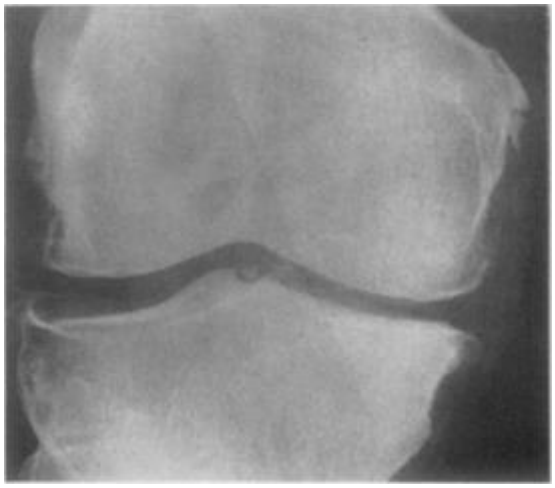
- **grade 0**: no radiographic features of OA are present
- **grade 1**: doubtful joint space narrowing (JSN) and **possible osteophyte**
- **grade 2**: **definite osteophytes** and possible JSN on anteroposterior weight-bearing radiograph
- **grade 3**: multiple osteophytes, **definite JSN,** sclerosis, possible bony deformity
- **grade 4**: large osteophytes, marked JSN, severe sclerosis and **definite bony deformity.**

Table 2.2: RADIOLOGICAL ASSESSMENT OF OSTEO-ARTHROSIS BY J. H. KELLGREN AND J. S. LAWRENCE



Grade 1

Grade 2



Grade 3

Grade 4

2.1.4 RISK FACTOR OF KNEE OSTEOARTHRITIS

The aetiology appears to be a combination of local and systemic factors. Several risk factors have been identified. Local factor such as obesity, elderly and joint injury while systemic factors such as genetics, hormones and bone density (Felson et al 2000).

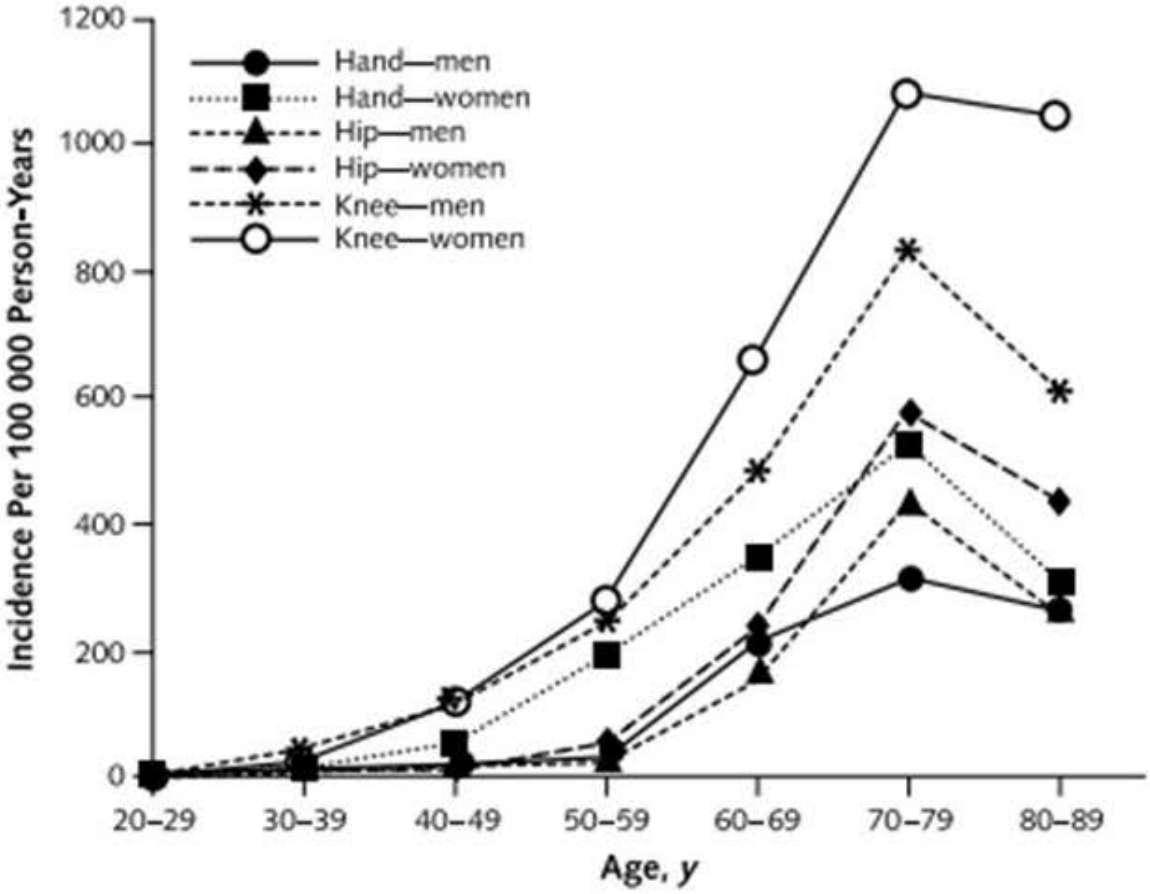
Recent study by Blagojevic, which was through systemic review and meta-analysis showed the main factors consistently associated with knee OA were obesity (pooled OR 2.63, 95% CI 2.28-3.05), previous knee trauma (pooled OR 3.86, 95% CI 2.61-5.70), hand OA (pooled OR 1.49, 95% CI 1.05-2.10), female gender (pooled OR 1.84, 95% CI 1.32-2.55) and older age (Blagojevic et al 2010).

With regard to gender, several studies have shown that radiographic knee OA is more common in women than in men. In the United States, the prevalence of radiographic knee OA in adults older than 60 is 42.1% in women and 31.2% in men (Dillon et al 2006). In Japanese patients aged 60 to 69 years, the prevalence of radiographic knee OA is 57.1% in women and 35.2% in men (Yoshimura et al 2009).

With regard to age, epidemiologic studies have shown that radiographic and symptomatic knee OA is much more common in the elderly, specifically individuals 60 years of age and older (Blagojevic et al 2010). There are two studies that have shown that knee OA prevalence is even greater in patients 85 years of age and older (Dillon et al 2006 , Yoshimura et al 2009).

Other risk factors are previous meniscectomy which are associated with advance age and obesity (Euglung and Lohmander et al 2004). However in recent years evidence showed there is growing for the importance of hormonal, bone density and genetic.

Figure 2: incidence of osteoarthritis of hand, hip, and knee in members of Fallon Community Health Plan, 1991- 1992, by age and sex. Clinical Practice Guidelines on the Management of Osteoarthritis 2002.



2.1.4.1 SYSTEMIC RISK FACTOR OF OSTEOARTHRITIS

1) Ethnicity

There are many studies regarding systemic risk factor, to show why elderly women are more likely to have osteoarthritis compare to male (Hirsch et al 2010, NHANES 1 and 3).

Two studies have specifically examined ethnic differences in radiographic knee OA mainly in African American and Caucasians. Result from one large National study, the NHANES I (National Health and Nutrition Examination Survey I) 1988, found that African American women were twice as likely to exhibit radiographic knee OA as Caucasian women, while there was no significant difference between African American and Caucasian men (Anderson and Felson et al 1988). However another study from the rural south, The Johnston Country OA Project, suggests there are no significant differences in groups of both ethnic for this disease (Jordan et al 1995).

2) Hormonal density

One of systemic risk factor that leads to osteoarthritis among women is hormonal status and bone density. Cohort studies have reported that women taking estrogen have decreased prevalence and incidence of radiographic osteoarthritis (Nevit et al 1996, Zhang et al 1998). However, case–control studies evaluating current or past estrogen use in women with and those without symptomatic osteoarthritis have been inconsistent in their findings; as a result, the current evidence is at best only suggestive of a protective effect of estrogen on osteoarthritis (Oliveria et al 1996, Sandmark et al 1998).

Furthermore, any protective effect might be confounded by healthy habits of estrogen users, which might protect them from disease. It was also suggested that estrogen deficiency plays are role in causing the disease. It may accelerate the disease progression.

Women with lifetime high exposure to endogenous and exogenous estrogen have high bone mass which as noted above, appears to increase the risk for knee and hip osteoarthritis. This indirect effect of estrogen could counteract the protective effect of estrogen on osteoarthritis suggested by some studies. Besides that, for women with osteoarthritis, estrogen exposure could slow the subchondral bone changes and bone turnover that are associated with progression of knee and hip osteoarthritis. These arguments suggest the complex conflicting roles of estrogen in osteoarthritis. Thus, hormonal factors are thought to play a role in the pathogenesis of osteoarthritis.

In the new evolution of research, the relationship of the index to ring finger length ratio (2D:4D) with osteoarthritis is studied. It is related with to prenatal exposure of hormone (androgen) which is maybe corresponding with tendency and severity of knee OA in elderly. This issue will be discussed further in the next sub chapter.

2.1.4.2 BODY MASS INDEX (BMI) AND KNEE OSTEOARTHRITIS

Persons who are overweight have a high prevalence of knee osteoarthritis. For many years, it was not clear whether being overweight preceded or was a consequence of osteoarthritis, given the immobility and disability the disease can produce. Recent studies have proved that being overweight antedates the development of disease (Menninen et al 1997, Felson et al 1997). Furthermore, in persons with osteoarthritis, being overweight increases the risk for radiographic progression (Daugados et al 1992, Shcauten et al 1992).

In most studies, the increased risk for osteoarthritis of the knee among overweight persons is stronger in women than men (Felson et al 1998). Tucker et al 2008 study showed the association between overweight or obesity and health problems of the lower extremities, ex; osteoarthritis; pain of the knee or hip, and disability in walking. Among patients with osteoarthritis and chronic pain, both moderate overweight and obesity are associated with disability in walking.

Research on the association between BMI and symptomatic knee osteoarthritis showed more consistent result. The French and Finnish National studies and the Third National Health and Nutritional Examination Study all found a strong link between BMI and knee OA disability.

In persons who are overweight, weight loss can reduce the risk for osteoarthritis. In the Framingham Study, an observational study, women who lost an average of 11 lbs decreased their risk for knee osteoarthritis by 50% (Felson et al 1992). However the effect of weight loss on symptoms in persons with knee osteoarthritis has not been well studied. One small randomized trial of an appetite suppressant showed that the amount

of weight loss was strongly correlated with improvement in symptoms and signs of osteoarthritis (William et al 1981).

For each 1-lb increase in weight, the overall force across the knee in a single-leg stance increases 2 to 3 lb. This load effect probably explains most of the increased risk for osteoarthritis of the knee and hip among overweight persons (Congon et al 2001).

One of objective in my study to evaluate relationship between BMI and disability through WOMAC score in women with knee osteoarthritis followed by association with 2D:4D length ratio.

2.2 2D:4D LENGTH RATIO

2.2.1 OVERVIEW OF 2D:4D LENGTH RATIO

The disproportionate length of human fingers has generated much interest among researchers. The lengths of the second digit (2D) and fourth digit (4D) have received the greatest attention, because of the noted sex differences (Peters et al 2002).

Difference finger length (index and middle finger) extent patterns in humans (Peters et al., 2002). The sex differences have generally been tested by expressing the pattern as 2D to 4D (2D:4D) ratio.

In accordance with the 'Manning hypothesis', the 2D:4D ratio of the human hand is a sexually dimorphic trait. Sexual dimorphism is the condition where the two sexes of the same species exhibit different characteristics and capability beyond the differences in their sexual organs themselves.

Generally, males have low 2D:4D ratio; a ring finger that is longer than their index finger .While female typically have high or equal 2D: 4D ratio; index finger longer than ring fingers or the same length (Manning et al 2000). There is evidence that relative digit length is fixed in utero by about the 14th week of pregnancy (Garn et al 1975).

Visually, 2D: 4D finger length ratio can classify to three types, 1) type I which is index finger longer than ring finger, 2) type II; index finger equal to ring finger and 3) type III; index finger shorter than ring finger (Zhang et al 2008).

In 1983 Dr Glenn Wilson of King's College, London published a study examining the correlation between assertiveness in women and their digit ratio. This

was the first study to examine the correlation between digit ratio and a psychological trait within members of the same sex.

In 1998, John T. Manning and colleagues reported the sex difference in digit ratios was present in two years old children and further developed the idea that the index was a marker of prenatal sex hormones. The hormonal level of the prenatal environment was estimated indirectly using a recently suggested indicator of in utero hormone levels: the second to fourth digit ratio (2D:4D ratio). Since then research on the topic has evoked around the world.

Manning have pointed out that prenatal exposure to testosterone and estrogen may leave morphological markers (Manning et al 2002). A fetus is exposed to prenatal testosterone from two sources: the fetal testes and adrenal glands. The main source of prenatal estrogen comes from the adrenal glands and the placenta through the aromatase conversion of testosterone (George et al., 1981).

These fetal sources of steroids are highly dependent on the differentiation process of fetal gonads (Lording and De Kretser et al 1972). The differentiation of the fetal gonads is controlled by Homeobox or Hox genes (Za´ka´ny and Duboule et al 1999). In particular, the posterior-most Hox D and Hox A genes are strongly expressed in the urogenital system, including the gonads. However, these genes are also required for the growth and differentiation of digits and toes (Kondo et al 1997, Scutt et al 1998). The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen (Scutt et al 1998).

Strong evidence for the role of androgen comes from the association between the 2D:4D ratio and congenital adrenal hyperplasia (CAH), a condition of elevated androgen production, as both males and females with CAH have type III finger pattern

than controls (Brown WM et al 2002). Also female dizygotic twin fetuses growing next to males were found to have lower ratio than the ones growing next to females suggesting the influence of some level of androgen diffusion (Van Anders SM 2006).

A variety of behaviour that are either sexually dimorphic or ascribed to the actions of sex steroids also correlate with 2D:4D (Manning et al 2002).

In general, type I finger pattern, which is female pattern will show feminization such as gentleness, less aggressiveness, less physical ability, increase risk for obesity and others. While type III which is male type, show more masculinization and producing typical male behaviour and capability such as roughness, aggressive, good performance in sport but less in academic, more tolerance to pain and good leadership.

Table 2.3: Correlation between digit ratio and traits.

	Low 2D:4D ratio or type III	High 2D:4D ratio or type I
Physiology and disease		• Lowered sperm counts (Manning et al 1998) • Increased risk for heart disease in males (Manning et al 2001) • Increased risk of obesity and metabolic syndrome in males (Fink et al 2006) • Reduced risk for prostate cancer (Walsh et al 2010) • Reduced birth size in males (Roland et al 2002,Klimak et al 2014)
Psychological disorders	•Increased rate of ADHD in males (Fadden et al 2005) •Increased rate of Asperger syndrome and other autism spectrum disorders (when comparing digit ratio to general population (Manning et al 200) •Reduced risk in females for anorexia nervosa (Klump et al 2006) and in males for eating disorders (Smith et al 2009)	• Increased risk for depression in males (Bailey et al 2004) • Increased rate of schizophrenia (Arato et al 2004) • Increased rate of psychopathy in females (Blanchard et al 2010) • Reduced risk of alcohol dependency (Komhuber et al 2011) • Reduced risk of video game addiction (Komhuber et al 2013) • Increased anxiety in males (Evardone et al 2009)
Physical and competitive behavior		• Reduced financial trading ability (Coates et al 2009) • Right handedness skills (Fink et al 2004) • Reduced performance in sports (Manning et al 2001)
Cognition and personality	•Assertiveness in female (Wilson et al 1983) •Aggression in males (Bailey et al 2005) •Masculinity of handwriting (Beech et al 2005) •Academic performance (Nye et al 2003)	• Personality traits correlated with digit ratio, higher being more feminized (Austin et al 2002) • Higher exam scores among male students (Romano et al 2006)

Table 2.3, continued.

Management	•Leadership (Derval et 2010) •Innovation (Derval et al 2010)	
Sensory perception		• Smell perception (Derval et al 2010) • Color perception (Derval et al 2010) • Tactile perception (Derval et al 2011)

2.2.2 2D:4D LENGTH RATIO AND OSTEOARTHRITIS

Several studies of 2D:4D ratio and the risk of knee osteoarthritis have been done before. Initial study started by Zhang et al 2008, to determine relationship between 2D:4D length ratio and risk of knee and hip osteoarthritis, showed significant association between type III "male" pattern with OA, especially knee OA. The risk was greater in women with more than 2.5 times compared to male. It was not associated with any physical activity or male hormone surrogates. This new identified risk factor assumed as independent of other major OA risk factors.

A year later, another study proposed by Ferraro et al 2009, to quantify between 2D:4D length ratio and other site of osteoarthritis (hand, foot, and cervical). Interestingly, result was consistent with previous study and more significant with knee osteoarthritis in women. The biology of this phenomenon is complex. And it is possible of genetic linkage which predisposed type III "male pattern" to knee osteoarthritis.

Prenatal testosterone exposure maybe a key point. Furthermore it has been proposed that the Homeobox (Hox) genes, specifically those of the Hox A and Hox D groups involved in growth of bone, cartilage and soft tissue of appendages. Other literature also showed women with type III, has more physically risky behaviour, which may lead to joint trauma and eventually osteoathritis (Manning et al 2001, Haugen et al 2011).

Not all researchers have come to the same conclusion regarding this matter. Cross sectional study using large community database, found an association between type III finger pattern and knee injury in men. However, this study did not find significant associations with risk of knee osteoarthritis with 2D:4D length ratio (Haugen et al 2011). Although the relationships between knee joint trauma and development of

post-traumatic osteoarthritis remain poorly understood, it is clear that articular surface fractures, joint dislocations, and ligament and meniscal ruptures may lead to increased risk for later osteoarthritis (Buckwalter et al 1997, Honkonen et al 1995). Apparent risk factors for posttraumatic osteoarthritis include high body mass, high level of activity, residual joint instability or malalignment, and persistent articular surface incongruity.

Paradowski looked for association between 2D:4D length ratio with knee osteoarthritis and progression after meniscectomy also concluded lack of relationship between both of it as previously published (Paradowski et al 2013). However, in this study relatively small proportion of women involved and the sample are small.

Due to the conflicting data regarding the association between the index to ring finger (2D:4D) length ratio and the risk of osteoarthritis, new researcher tried to conclude in a better way. There are two recent studies with large database, which done by Kristin and Sultana Monira which provide solid evidence regarding association type III finger pattern and risk severe knee and hip osteoarthritis in participants which under gone total joint replacement (Kristin et al 2013, Sultana Monira et al 2014).

Both study showed that significant associations between the type III finger pattern and total knee replacement but not the risk of hip replacement. The site difference in OA risk in relation to 2D:4D may be explained, at least in part, by the different susceptibility of knee and hip OA in response to injury. The Johns Hopkins Precursors Study, a prospective study conducted in medical students, revealed that early knee injuries were associated with a 2.95 times relative risk of symptomatic knee osteoarthritis, with no association between hip injuries and later development of hip osteoarthritis.

Moreover, this study reported higher prevalence and incidence of knee injury than hip injury, indicating that the knee is more prone to injury than the hip.

2.3 KNEE OSTEOARTHRITIS AND PHYSICAL DISABILITY

Current insights about disease and personal factors associated with a high risk for physical disability are based chiefly on cross-sectional studies. Factors linked to disability in patients with osteoarthritis include pain (Slemenda et al 1997, Jordan et al 1997); psychosocial factors, such as depressive symptoms (Rajeski et al 1996, Van Barr et al 1998); muscle weakness (Allindon et al 1993); poor aerobic capacity (Rajeski et al 1993) ; and in some studies radiographic disease severity (Sharma et al 1998).

A better understanding of the causes of disability in osteoarthritis will facilitate the development of preventive strategies. The disease disability relationship in osteoarthritis has been examined by using conventional radiography. Examination of specific anatomic and physiologic features of osteoarthritis, many of which are not revealed by radiography, may better elucidate the role of disease events in functional decline. It is important to separate conceptually the disease process of osteoarthritis and the syndrome of musculoskeletal pain and disability; the two are only weakly correlated (Sharma et al 1998).

Whereas osteoarthritis is associated with increasing age, obesity, injury, previous deformity, and ligamentous laxity, the broader clinical problem of musculoskeletal pain and disability is predicted by increasing age, osteoarthritis, obesity, lack of exercise, low personal self-efficacy, comorbid conditions caused by smoking, alcohol, and other risk factors; depression, low educational level, and poor socioeconomic status (Fries et al 1997, Vita et al 1998). Many of these risk factors for musculoskeletal pain and disability can be altered.